REMARKS

Claims 1- 47 are pending. Claims 8-47 have been withdrawn by the Examiner, under 37 C.F.R. § 1.142(b) as being directed to a non-elected invention. The previous rejections under 35 U.S.C. § 101 have been withdrawn in view of Applicant's amendments to the claims. The previous rejection under 35 U.S.C. § 112, second paragraph, have been withdrawn in view of Applicant's amendments to the claims. The previous rejection under 35 U.S.C. § 112, first paragraph, has been withdrawn in view of Applicant's amendments to the claims.

The Examiner has confirmed that Applicant claims the benefit of priority of USSN 60/391,514 filed June 25, 2002.

Claim 1 has been amended to include the subject matter of claim 2. Claims 2, 5 and 6 have been canceled so as not to duplicate subject matter. Claim 4 has been amended to include the subject matter of claims 5 and 6 and to include the term "human antibody." Support for this amendment is found throughout the specification. The paragraph numbering is taken from the published application (US 2004/0057956). For example, paragraph [0076] refers to human antibodies; paragraphs [0013] to [0014], paragraphs [0094] to [0094], and paragraphs [0120] to [0124] which describe the use of peptides injected *in vivo* to a human patient to generate antibodies; paragraphs [0110] to [0116] which describe the use of vectors expressing the peptides for administration to a patient in order to generate specific antibodies. No new matter has been added by these amendments and entry is respectfully requested. Amendment or cancellation of subject matter is not to be construed as surrender of any subject matter. Applicant hereby reserves the right to pursue the amended or canceled subject matter in one or more continuation or divisional applications.

Claim Rejections Under 35 U.S.C. § 102

Claims 1 and 4-7 were rejected under 35 U.S.C. § 102(e) as anticipated by Rosen et al., (US 20030054421) as evidenced by Bost *et al.* (*Immunol. Invest.* 1988; 17:577-586) and Bendayan *et al.* (*J. Histochem. Cytochem.* 1995; 43:881-886) and the instant specification at page 3, 3rd paragraph and page 43-44, for reasons of record as put forth in the Office Action mailed May 17, 2007.

Applicant respectfully traverses.

The Examiner has acknowledged that the antibodies of Rosen may or may not bind the RSATEEEPPND amino acid sequence. The Examiner, however, continues to assert that Rosen "not only teaches antibodies against SEQ ID NO: 745 as a whole, which is 94% identical across residues 1-707 of the Rat NaK ATPase sequence obtained from Genbank accession number AAAA416781 wherein the Rat Genbank sequence comprises SEQ ID NO: 1 of the instant application." The Examiner asserts that the antibodies of Rosen would "cross-react" with the instant peptides and thus anticipate the instant invention. Applicant respectfully disagrees.

As discussed previously, and reiterate here, it is well known in the art that one amino acid change to a sequence may abolish binding. The Examiner cites Rosen in view of Bost and Bendayan to allege that the peptide "TEEEPQNDN" of Rosen, in view of Bost peptides "LEHLLL" and LERILL" would imply that Rosen teaches the instant antibodies. Further the Examiner alleges that "the extensive homology (94%) across the full length SEQ ID NO: 745 residues 1-707 of the Rat NaK ATPase, as well as Rosen's teachings about antigenic epitopes of SEQ ID NO: 745 which are 100% identical to Rat NaK ATPase, the antibodies of Rosen

necessarily recognize the amino acid sequence comprising RSATEEEPPNDD..." Applicant respectfully disagrees.

As discussed in the previous response, Applicant teaches antibodies which bind to a specific sequence. The Examiner alleges that the antibodies in the cited references would bind to the instant sequences. First, the sequences are not the same. The Examiner is basing his arguments on probabilities, in that out of 707 amino acids, antibodies could probably be generated which probably could bind to the sequences disclosed in the instant invention. "To establish inherency, the extrinsic evidence must make clear that the missing descriptive matter is necessarily present in the thing described in the reference and that it would be so recognized by persons of ordinary skill." *In re Robertson,* 169 F.3d 743, 745 (Fed. Cir. 1999) (citing *Continental Can Co. v. Monsanto Co.,* 948 F.2d 1264, 1268 (Fed. Cir. 1991)). "Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient." *Id.* Notably the Federal Circuit recently elaborated on inherency in the complex arts. "Particularly when the science or technology is new or complex, a bare suggestion or hope that requires significant experimentation for implementation or verification is not an invalidating 'anticipation' of that which is ultimately achieved." *Phamastem Therapeutics, Inc. v. Viacell, Inc.,* 2007 *U.S.* App. LEXIS 16245, 79 (Fed. Cir. July 9, 2007).

Not only are the sequences taught by Applicant at least 42% non homologous to the Examiner's cited peptide, the differences are also qualitative. That is, the instant sequence comprises amino acids which fall in different groups as those indicated in the sequence by the Examiner e.g. charged amino acids versus uncharged amino acids, the instant antibodies also induce a physical and chemical reaction causing the myocytes to contract. Additionally, Applicant notes that the two amino acids substituted in Bost did not change the polarity or pH of the sequence, because a polar, basic histidine was substituted for a polar, basic arginine at

one site, and a nonpolar, neutral leucine was substituted for a nonpolar, neutral isoleucine at the other site. Applicant notes that the differences between the cited art sequences and the amino acid sequence represent fundamental changes in the characteristics of the amino acid side chains. Specifically, a polar glutamine is substituted for a non-polar proline and a neutral asparagine is substituted for an acidic aspartic acid. Thus, the antibodies which would be generated would not be the same as they recognize different sequences.

Second, the length of the sequence between the instant invention and the Examiner's asserted sequence is at least 25% longer. Third, the instant antibodies not only bind to the instant sequence, but binding of the antibodies to the instant sequence induce myocyte contraction and increase in Ca^{2+}. See, for example, Figures 2-6 and Examples 1 and 2. Neither Rosen, standing alone or in combination with Bost and Bendayan, teach the instant sequences, nor the antibodies that bind to the instant sequences, nor that the antibodies are inotropic antibodies. Even assuming *arguendo*, that the antibodies of Rosen cross-react with the instant sequences as alleged by the Examiner, these antibodies do not increase myocyte contraction nor increase in Ca^{2+}. Rosen in view of Bost and Bendayan do not teach or disclose inotropic antibodies, nor would any combination of references teach antibodies that induce myocyte contraction. However, without acquiescing to the Examiner's rejection and to compact and expedite prosecution, Applicant has amended claim 1 to include the subject matter of claim 2. As such, the cited references fail to teach each and every claim limitation.

In view thereof, Applicant respectfully requests reconsideration and withdrawal of the instant rejection.

Claims 1, 4 and 7 were rejected under 35 U.S.C. § 102(b) as anticipated by Ball *et al.*, (*Biochim. Biophys. Acta.* 1987 Nov 5;916(1):100-11) as evidenced by Bost *et al.* (*Immunol. Invest.* 1988; 17:577-586) and Bendayan *et al.* (*J. Histochem. Cytochem.* 1995; 43:881-886)

and as further newly evidenced by Harlow *et al.* (Antibodies, Cold Spring Harbor Press, pp. 72-78 (1988)).

Applicant respectfully traverses.

Ball *et al.* recite an amino acid sequence which is qualitatively different than the instant sequence. The amino acids differ in that non polar alanine is present in the sequence cited by the Examiner. As is known in the art, antigen-antibody interactions are the result of complementarity in shapes, hydrophobic interactions, hydrogen bonds and Van der Waals forces. The Examiner points to Harlow as "evidence" that "the polyclonal antibodies of Ball bind to a sequence of amino acids with 6 centrally located residues 100% identical to centrally located residues of SEQ ID NO: 1." Applicant respectfully disagrees. It is well known in the art that even though 6 amino acids may generate an antibody, it does not necessarily mean that this antibody would be cross reactive. As indicated in Harlow, page 76 paragraph 2: "[w]ith peptides of 6 amino acids or slightly larger, the responses vary. Some will generate good antibodies and some will not." Furthermore, even assuming *arguendo*, there is cross-reactivity as alleged by the Examiner, the binding affinity would most likely be weak as the charge of each sequence differs resulting in opposing forces which would contribute to lower affinities. In addition, neither of the cited references teach antibodies which bind to the instant sequence and cause myocytes to contract as taught by Applicant.

In view thereof, Applicant respectfully requests reconsideration and withdrawal of the instant rejection.

Claims 1-3, 5 and 7 were rejected under 35 U.S.C. § 102(b) as being anticipated by Arystarkhova *et al.* (*J. Biol. Chem.* 1992 Jul 5;267(19):13694-701) as evidenced by Bost *et al.*

(*Immunol. Invest.* 1988; 17:577-586) and Bendayan *et al.* (*J. Histochem. Cytochem.* 1995; 43:881-886).

Applicant respectfully traverses.

The Examiner alleges that "Arystarkhova teaches that the Vg4 antibody binds an epitope composed primarily of contiguous amino acids QAATEEEPQNDNL of pig α1 NaK ATPase, wherein the 'crucial' EEEP residues are conserved between rat α1 and porcine α1 NaK ATPase AND Arystarkhova further teaches that Vg4 does indeed bind rat α1 NaK ATPase with an affinity slightly lower than its affinity for porcine α1 NaK ATPase." Applicant respectfully disagrees. The Examiner asserts that the "crucial" binding for VG4 are the residues EEEP. This does not mean, however, that these same residues would be crucial for the instant antibodies as these antibodies not only are specific for the peptide of the instant invention, but these antibodies are inotropic antibodies. Thus, even if, assuming *arguendo*, VG4 did bind the instant sequence, neither Arystarkhova nor the combination of references teach or disclose that their antibodies are inotropic antibodies and as such do not meet each claim limitation. As to the Examiner's assertions that there is a slight reduction in affinity regarding substitution of serine for Ala^{112} or proline for Gln^{119}, Applicant respectfully disagrees. The extracts against which VG4 was directed to in the assays described by Arystarkhova are crude microsomes subjected to enzymatic digestion and as such any number of sites could be exposed. The Examiner is basing the rejection on probabilities and possibilities that VG4 may bind the instant sequence, however, as discussed above, VG4 does not cause myocyte contraction and does not disclose each and every claim limitation.

In view thereof, Applicant respectfully requests reconsideration and withdrawal of the instant rejection.

Claim Rejections Under 35 U.S.C. § 103

Claims 1-3, 5 and 7 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Arystarkhova *et al.* (*J. Biol. Chem.* 1992 Jul 5;267(19):13694-701) in view of Rosen *et al.* (US 20030054421), Schwinger *et al.* (*Circulation.* 1999 Apr 27;99(16):2105-12), Mohraz *et al.* (*J. Biol. Chem.* 1994 Jan 28;269(4):2929-36), Bost *et al.* (*Immunol. Invest.* 1988; 17:577-586), Bendayan *et al.* (*J. Histochem. Cytochem.* 1995; 43:881-886).

Applicant respectfully traverses.

The Examiner alleges that "Arystarkhova teaches that the Vg4 antibody binds an amino acid sequence comprising RSATEEEPPNDD, i.e. Rat α1 NaK ATPase, and teaches that residues EEEP, which are conserved between the rat α1 and pig α1 NaK ATPase, are crucial for Vg4 binding. Thus, the Vg4 antibody of Arystarkhova is an antibody which recognizes an amino acid sequence comprising RSATEEEPPNDD, and is a humanized Vg4 antibody will have the same epitope specificity." Applicant respectfully disagrees. As discussed above, one amino acid change in a peptide sequence can result in loss of specificity. Indeed, Arystarkhova confirms that replacing of glutamine with glycine in chicken α1 "nearly abolished antibody binding altogether." (See, page 13700, col. 2, top paragraph). Furthermore, Arystarkhova does not teach or disclose that VG4 binds the instant sequence. Figure 7, indicates that the VG4 was tested against crude microsomes and hence any number of peptides and epitopes are present in the crude extract. One of ordinary skill in the art would not conclude that the antibodies taught by Applicant and the VG4 of Arystarkhova are similar. Furthermore, the cited references fail to supplement the deficiencies of Arystarkhova. The Examiner cites Arystarkhova in view of Rosen *et al.* (US 20030054421), Schwinger *et al.* (*Circulation.* 1999 Apr 27; 99(16):2105-12), Mohraz *et al.* (*J. Biol. Chem.* 1994 Jan 28;269(4):2929-36), Bost *et al.* (*Immunol. Invest.* 1988; 17:577-586), and Bendayan *et al.*, (*J. Histochem. Cytochem.* 1995; 43:881-886) and alleges that these references "teach" that

antibodies cross-react and therefore bind to similar sequences. As discussed above, it is unknown whether VG4 antibody actually binds to the instant sequence (RSATEEEPPNDD) and the cited references do not cure any of the deficiencies in Arystarkhova to teach that VG4 antibody binds the instant sequence. Even assuming *arguendo*, that VG4 binds the instant sequence, neither Arystarkhova standing alone or in view of Rosen *et al.* (US 20030054421), Schwinger *et al.* (*Circulation.* 1999 Apr 27; 99(16):2105-12), Mohraz *et al.* (*J. Biol. Chem.* 1994 Jan 28;269(4):2929-36), Bost *et al.* (*Immunol. Invest.* 1988; 17:577-586), and Bendayan *et al.*, (*J. Histochem. Cytochem.* 1995; 43:881-886) teach the instant antibody which cause myocyte contraction. As the Federal circuit has stated, "[t]he mere fact that the prior art may be modified in the manner suggested by the Examiner does not make the modification obvious unless the prior art suggested the desirability of the modification." *In re Fritch*, 972 F.2d 1260,1266, 23 USPQ2d 1780, 1783-84 (Fed. Cir. 1992). Obviousness may not be established using hindsight or in view of the teachings or suggestions of the inventor. *Para-Ordance Mfg. v. SGS Importers Int'l, Inc.*, 73 F.2d 1085, 1087, 37 USPQ2d 1237, 1239 (Fed. Cir. 1995). One of ordinary skill in the art would not arrive at the conclusion, based on the combination of references, that an antibody specific for one sequence, would also bind to another sequence. As is known in the art, antibody-antigen binding is based on several mechanisms, e.g. Van der Waal's forces, polarity, size, affinity, avidity etc.

To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on

applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). MPEP 2142.

As set out above, Arystarkhova in view of the above-references does not teach or suggest all of Applicants claim limitations. In particular, Arystarkhova is silent with respect to binding of the antibody to the instant sequence and resulting myocyte contraction. Further, the specificity of the antibodies for the instant sequence taught by Applicants is not inherent in Arystarkhova. Arystarkhova describes the "cross reactivity" of the VG4 against crude extracts of microsomes, which drops precipitously with a 1 fold dilution. As clearly demonstrated in Applicants' specification the inotropic antibodies are specific for RSATEEEPPNDD and when the antibodies bind this sequence, the binding results in myocyte contraction. Furthermore, none of the references provide any teaching, direction or motivation to one of ordinary skill in the art to combine them and arrive at the instant invention. None of the references teach or disclose the affinity of the antibodies for the "cross reactive" epitopes, none of the references teach an antibody directed to the specific sequence, and none of the references teach inotropic antibodies. Thus, reading any one of these references alone or in combination, would not motivate one of ordinary skill in the art to even suggest that an antibody can function as an inotropic antibody, with the resulting therapeutic properties.

In view thereof, Applicants respectfully request reconsideration and withdrawal of the instant rejection.

CONCLUSION

In view of the foregoing, reconsideration and withdrawal of all rejections and allowance of the application is respectfully solicited.

If there are any remaining issues or the Examiner believes that a telephone conversation with the undersigned would be helpful in expediting prosecution of this application, the Examiner is invited to call the undersigned at telephone number shown below.

Although, Applicant believes that no further extensions of time are required with submission of this paper, Applicant requests that this submission also be considered as a petition for any extension of time if necessary. The Commissioner for Patents and Trademarks is hereby authorized to charge the amount due for any retroactive extensions of time and any deficiency in any fees due with the filing of this paper or credit any overpayment in any fees paid on the filing or during prosecution of this application to Deposit Account No. 04-0100.

Respectfully submitted,

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Nicholas A. Zachariades, Ph.D.
Registration No. 56,712
Darby & Darby P.C.
P.O. Box 770
Church Street Station
New York, New York 10008-0770
(561) 626-2222
(212) 527-7701 (Fax)
Attorneys/Agents For Applicant

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